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Parallel synthesis and SAR study of novel oxa-steroids as potent and selective progesterone receptor antagonists

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Abstract—Efficient parallel synthesis of novel 7-oxa-steroids **4** has been achieved from the key intermediate **3** via a one-pot four-step sequence. oxa-Steroids **4** with various *ortho*-, *meta*-, and *para*-monosubstituents on the phenyl ring, as well as disubstituted phenyl and heterocycles, were evaluated for progesterone receptor (PR) and glucocorticoid receptor (GR) antagonist activities. SAR study demonstrated that the *para*-fluorinated substituents on the phenyl ring not only increased the potency for PR in a T47D cell functional assay, but also improved the selectivity over GR in an A549 cell functional assay. The *para*-fluorophenyl oxa-steroid **4l** and the *para*-trifluoromethylphenyl oxa-steroid **4p** were found to be remarkably more potent and more selective PR antagonists than mifepristone, with subnanomolar potency and about 140-fold selectivity over GR. Molecular modeling of the oxa-steroid bound to PR provided meaningful insight for the SAR study. oxa-Steroids **4a** and **4b** were found to be more efficacious than mifepristone in vivo in a rat uterine complement C3 assay via the oral route, although they were less than or equally potent to mifepristone in the T47D assay.

The progesterone receptor (PR), like other steroid receptors, plays a unique and crucial role in mammalian development and homeostasis. Progesterone is known to be required for mammary gland development, ovulation, and the maintenance of pregnancy. It has less clearly defined functions in bone, the cardiovascular system, and the central nervous system. In terms of opportunities for pharmacological intervention, it has arguably the greatest unexploited potential of the steroids. Currently, steroidal progestin agonists and antagonists are clinically approved for contraception, hormone replacement therapy, and therapeutic abortion. There is strong preclinical and clinical evidence for the value of progestin antagonists for treating endometriosis, uterine fibroids, dysfunctional uterine bleeding, and breast cancer.[1]

The discovery of the first PR antagonist, mifepristone (RU-486),[2] has stimulated an intensive search for more potent and selective antiprogestins. This has led to the identification of a variety of steroidal[3] and nonsteroidal[4] PR modulators in the past years. However, current PR antagonists, such as mifepristone, are compromised as clinically useful agents due to overt glucocorticoid receptor (GR) antagonism.[5] Therefore, new compounds with antiprogestational activity devoid of antiglucocorticoid activity are highly desirable for both clinical applications and basic endocrine research.[6] The recent discovery that treatment of mifepristone can potentially prevent *BRCA1*-mediated breast cancer[7] makes it more urgent to discover novel potent and selective PR antagonists to address unmet medical needs.

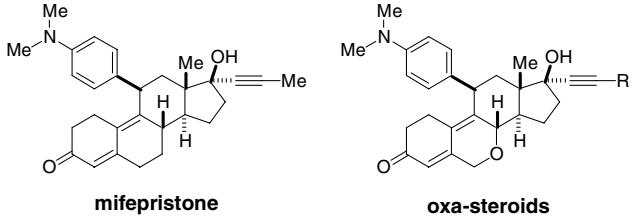

Figure 1. Structures of mifepristone and oxa-steroids.

Keywords: Progesterone; Receptor; Antagonist; oxa-Steroid; Glucocorticoid; Parallel synthesis; SAR study; In vitro; In vivo.
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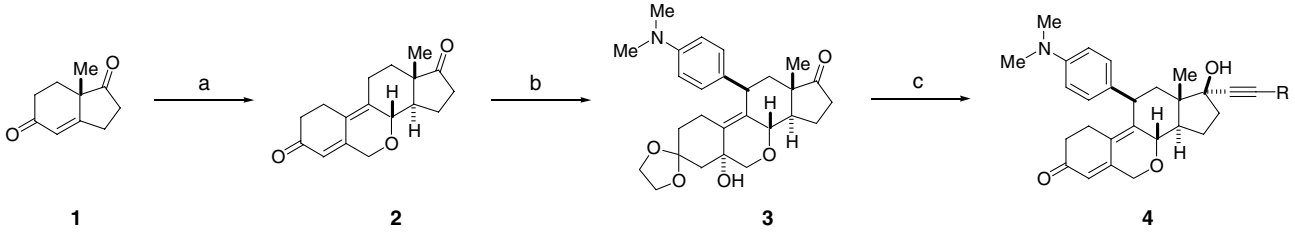
We have recently achieved the first synthesis and identification of novel 7-oxa-steroids as promising potent and selective PR antagonists (Fig. 1).[8] Herein we report the parallel synthesis and SAR study of a series of new oxa-steroids along this line for the development of potent and selective PR antagonists.

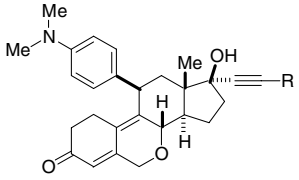
The oxa-steroids **4** were synthesized from (8*S*,13*S*,14*R*)-7-oxa-estra-4,9-diene-3,17-dione **2** (Scheme 1),[8] which was prepared from the Hajos–Parrish ketone **1**.[9] It is interesting to note that the synthesis of oxa-steroids **4** with five chiral centers in the congested heteropolycyclic structure was efficiently achieved in a highly stereoselective fashion, with the stereochemistry of the four new chiral centers being excellently controlled by the single chirality of the starting material, the Hajos–Parrish ketone **1**.

The mifepristone-like oxa-steroid **4a** has an IC_{50} of 7.5 nM for PR and over 10-fold selectivity over GR. Although it is less potent than mifepristone, it is slightly more selective than the equipotent mifepristone (Table 1). A preliminary SAR study at the C17-ethynyl position with various substituents has led to the discovery of the remarkably more potent and more selective PR antagonist **4b** with the phenyl group at the C17-ethynyl position. Compound **4b** has an IC_{50} of 1.4 nM for PR and over 200-fold selectivity over GR.[8] Apparently,



Scheme 1. (a) Ref. 9; (b) Ref. 8; (c) parallel synthesis of oxa-steroids **4** via the one-pot four-step sequence. Reagents and conditions: (1) RCCH, LiHMDS, THF, rt, 15 min; (2) compound **3**, THF, rt, 4 h; (3) 3 N HCl aq, acetone, rt, 4 h, 60–80%.

Table 1. SAR study of oxa-steroids **4**



Compound	R	T47D (PR), IC_{50} (nM)	A549 (GR), IC_{50} (nM)	Selectivity (GR/PR)
Mifepristone	—	1.4	1.6	1
4a	Methyl	7.5	86.5	12
4b	Phenyl	1.4	304.0	217
4c	2-F–phenyl	1.4	65.1	47
4d	2-Cl–phenyl	1.1	64.8	59
4e	2-Br–phenyl	8.6	62.7	7
4f	2-Me–phenyl	5.8	113.2	20
4g	2-F_3C–phenyl	3.2	51.0	16
4h	3-F–phenyl	1.0	56.6	57
4i	3-Cl–phenyl	12.5	48.9	4
4j	3-Me–phenyl	2.9	36.3	13
4k	3-F_3C–phenyl	2.7	45.4	17
4l	4-F–phenyl	0.27	37.6	139
4m	4-Cl–phenyl	0.61	43.5	71
4n	4-Br–phenyl	0.94	31.3	33
4o	4-Me–phenyl	1.6	22.1	14
4p	4-F_3C–phenyl	0.75	111.0	148
4q	4-MeO–phenyl	3.2	80.3	25
4r	4-NC–phenyl	3.7	41.3	11
4s	4-Me_3C–phenyl	19.5	65.8	3
4t	3,5-di-F–phenyl	0.91	34.4	38
4u	2-Pyridyl	34.0	175.3	5
4v	3-Pyridyl	21.0	341.6	16
4w	4-Pyridyl	39.0	246.5	6
4x	3-Thienyl	1.6	56.0	35